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Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Polypharmacy is often regarded as a surrogate indicator of poor prescribing quality.
- Rates of polypharmacy are increasing.
- Polypharmacy is associated with adverse outcomes.

WHAT THIS STUDY ADDS

- Polypharmacy is associated with unplanned hospitalization.
- This effect is reduced in patients with multiple conditions, in whom only the most extreme levels of polypharmacy are associated with hospitalization.

AIMS

Prescribing multiple medications is associated with various adverse outcomes, and polypharmacy is commonly considered suggestive of poor prescribing. Polypharmacy might thus be associated with unplanned hospitalization. We sought to test this assumption.

METHODS

Scottish primary care data for 180 815 adults with long-term clinical conditions and numbers of regular medications were linked to national hospital admissions data for the following year. Using logistic regression (age, gender and deprivation adjusted), we modelled the association of prescribing with unplanned admission for patients with different numbers of long-term conditions.

RESULTS

Admissions were more common in patients on multiple medications, but admission risk varied with the number of conditions. For patients with one condition, the odds ratio for unplanned admission for four to six medications was 1.25 (95% confidence interval 1.11–1.42) *vs.* one to three medications, and 3.42 (95% confidence interval 2.72–4.28) for ≥10 medications *vs.* one to three medications. However, this effect was greatly reduced for patients with multiple conditions; amongst patients with six or more conditions, those on four to six medications were no more likely to have unplanned admissions than those taking one to three medications (odds ratio 1.00; 95% confidence interval 0.88–1.14), and those taking ≥10 medications had a modestly increased risk of admission (odds ratio 1.50; 95% confidence interval 1.31–1.71).

CONCLUSIONS

Unplanned hospitalization is strongly associated with the number of regular medications. However, the effect is reduced in patients with multiple conditions, in whom only the most extreme levels of polypharmacy are associated with increased admissions. Assumptions that polypharmacy is always hazardous and represents poor care should be tempered by clinical assessment of the conditions for which those drugs are being prescribed.

Introduction

Polypharmacy is an ill-defined term meaning the prescription of multiple medications and considered by some to indicate potentially inappropriate prescribing. It is commonly regarded as a surrogate measure of prescribing quality [1], based in part on the assumption that appropriate and safe prescribing includes rationalizing numbers of medications to avoid unnecessary use and reduce the potential for adverse reactions and unwanted drug interactions. However, rates of use of multiple medicines are increasing [2], driven by the increasing prevalence of multimorbidity [3], and a culture of single-condition guideline-driven prescribing [4].

Increasing numbers of prescribed medications have been associated with a range of adverse outcomes. These include high-risk prescribing [5], adverse drug reactions [6] and death [7]. Excessive numbers of medicines may contribute to poorer medication adherence [8], as well as being associated with lower quality of life [9].

It might be expected that medication-induced morbidity and poorer quality of clinical care associated with polypharmacy may result in unplanned hospital admissions. High use of primary and specialist ambulatory care and elective hospitalization may be seen as appropriate responses to managing ill health, whereas frequent unplanned admissions to hospital will often be undesirable. A number of studies have shown that polypharmacy is indeed associated with admission to hospital specifically for adverse drug reactions [10, 11]. However, there are relatively few large studies that have examined the association between polypharmacy and unplanned hospitalization more generally [12–14]. Furthermore, these studies have not examined how any such association varies with differing degrees of multimorbidity. In particular, we hypothesized that an increase in hospitalization with polypharmacy would be moderated in persons with greater health problems. This study seeks to describe better the association between polypharmacy, multimorbidity and hospital use, using linked routine clinical primary care and hospital data.

Methods

Study design

A retrospective cohort study was carried out using primary care data from 40 Scottish family practices, linked to admissions data for national acute care hospitals. All patients aged 20 years or more on 1 April 2006 were included in the study and followed up for 1 year for a record of an unplanned hospital admission.

Data sources

All 40 family practices contributing data to the Scottish Practice Team Information project, a national data set of clinical activity and morbidity, were included in the study. These practices are considered reasonably representative of the Scottish population [15], and the data they record are designed primarily to inform National Health Service (NHS) policy. Temporary registered patients were not included in the analysis. Practice clinical data, including patient demographic characteristics, electronic prescribing activity and diagnostic codes, were linked using probabilistic matching to admissions data for all Scottish hospitals (the Scottish Morbidity Record, SMR-01). Record matching was based on Soundex-encoded name, date of birth, sex, postcode and a unique nationwide identifier, the community health index (CHI). The linkage was carried out by the Information Services Division (ISD) of NHS National Services Scotland. The work was approved by the Privacy Advisory Committee of NHS National Services Scotland. The SMR-01 records are generated for all hospital discharges and transfers excluding accident and emergency department attendances, maternity and psychiatric admissions, and are considered of good quality for the study period [16]. We elected to include only adults (≥20 years old), because the nature of childhood morbidity and hospitalization may differ from that of adults.

Polypharmacy and multimorbidity

Prescriptions and clinical conditions were ascertained from the primary care records, based on the date 1 April 2006. Prescribing in UK general practice is conducted almost exclusively in an electronic manner, and so accurate records are captured of almost all prescriptions issued by a GP to a patient. We used a simple count of current prescriptions, irrespective of therapeutic class. Prescriptions were included in the count if they met the definition of an electronic record of a single drug available for repeated issue to the patient (in contrast to one-off prescriptions, such as short courses of antibiotics) and issued at least once within the previous year. We categorized the prescription count as none, one to three, four to six, seven to nine, and 10 or more medications. This was a pragmatic decision, based on a lack of consensus in the literature on defining polypharmacy and a wish to avoid dichotomization whilst maintaining simplicity and allowing for nonlinear effects of increasing medicine numbers. Throughout this paper, we have used the term 'polypharmacy' to mean 'multiple medications', without necessarily implying appropriateness of therapy or a specific minimum number of drugs. We used a list of 40 physical and mental health conditions identified from the primary care data to develop a measure of multimorbidity. The condition list, established by clinical expert consensus, sought to include morbidities recommended as core for any multimorbidity measure by a previous systematic review [17], diseases included in the UK primary care 'payment-for-performance' contract (Quality Outcomes Framework) and those considered important for health service planning by NHS Scotland. Importantly, the list

encompasses not simply high-morbidity/mortality conditions, but ones which may otherwise significantly impact on quality of life. The methods and definitions used for these 40 conditions have been previously described elsewhere in detail [3], and the list of conditions is given in Appendix 1. A simple, unweighted count of clinical conditions was used.

Outcomes

For all patients, we identified whether at least one unplanned hospital admission had occurred in the 12 month period 1 April 2006 and 31 March 2007, as recorded in SMR-01. Unplanned admissions are those classified as emergencies or urgent according to the clinical condition of the patient as assessed by the receiving physician. Unplanned admissions may or may not be instigated by the primary care doctor (general practitioner; GP).

Analysis

The proportions of patients with at least one unplanned admission were calculated for the whole population and by gender, age, deprivation quintile (Scottish Index of Multiple Deprivation; quintile 1 least deprived), number of clinical conditions and number of current prescriptions.

Fixed-effect univariable and mixed-effect multivariable logistic regression models were constructed for the outcome of unplanned hospital admission. Gender, deprivation, number of clinical conditions and number of prescriptions were modelled as categorical fixed-effect variables. Gender and socioeconomic deprivation were considered important confounders, owing to potential variations, such as baseline health status and disease severity, health-seeking behaviour, unmeasured factors (e.g. smoking, education status) and service provision, all of which may influence both prescribing and risk of hospital admission. Although we included all patients in the analysis, regardless of numbers of medicines, we treated one to three medicines, rather than none, as our baseline group, because this may better signify ongoing contact with the healthcare system, whereas patients with multimorbidity who are in receipt of no medicines may represent an unusual group. Age was modelled as a continuous fixed-effect variable, with an additional quadratic term, although the age-related distributions of numbers of medicines and admitted patients are presented in the tables as discrete age groups to simplify interpretation.

The association between prescribing and hospitalization may be expected to vary with the underlying degree of ill health. We therefore included an interaction term between clinical condition count and prescription count in the multivariable model. For this purpose, the number of clinical conditions was treated as a continuous version of the categorical main effect, and prescription count was treated as a categorical term.

Individual GP practices may vary in their tendency to admit patients, which has the potential to confound the association between prescribing and hospitalization. For example, GPs may have differing levels of experience of treating acute illness in the community or managing certain long-term conditions. The multivariable regression model therefore incorporated a random intercept effect for GP practice, to account for clustering of patients within practices.

It is possible that the way in which multimorbidity was quantified, or the type of admission, might have influenced the associations we observed between polypharmacy, multimorbidity and hospitalization. Therefore, we carried out sensitivity analyses, examining the effect of using a weighted count of conditions based upon the widely used Charlson index and changing the outcome from all unplanned admissions to potentially preventable unplanned admissions.

Analyses were conducted using Stata version 11.2 (StataCorp LP, College Station, TX, USA).

Results

A total of 180 815 patients were included in the analysis. The median age was 49 years (interquartile range 36–63 years), and 49.3% of patients were male. There were 61.9% of patients with at least one or more recorded long-term clinical condition, and 23.7% with three or more. The distribution of numbers of regular medications prescribed is shown in Table 1. Slightly under half of patients were prescribed at least one regular medication, with 25.2, 11.0, 5.9 and 4.6% receiving one to three, four to six, seven to nine, and 10 or more medications, respectively. Increasing numbers of regular medications are seen with female gender, older age, greater socioeconomic deprivation and increasing multimorbidity.

The proportions of patients admitted, including breakdown by age, gender, deprivation, morbidity and number of medications, are shown in Table 2. In the 12 month follow-up period, 10 828 (6.0%) patients had at least one unplanned admission. Of patients with six or more conditions, 26.5% had at least one unplanned admission, compared with 1.8% for those with no recorded long-term conditions. In the unadjusted models, there was strong evidence ($P < 0.001$) that increasing age, deprivation and numbers of clinical conditions were associated with increased admissions (Appendix 2). Hospitalizations were more common as numbers of prescribed medications increased; compared with the 5.2% of patients receiving one to three regular medications, unplanned admissions were experienced by 10.3% of patients receiving four to six medications [odds ratio (OR) 2.11; 95% confidence interval (CI) 1.98–2.24] and 24.8% of patients receiving 10 or more medications (OR 6.04; 95% CI 5.67–6.45).

Table 1

Percentage of patients on different numbers of regular medications

Percentage of patients on different numbers of regular medications	0	1–3	4–6	7–9	≥10
All patients	53.3	25.2	11.0	5.9	4.6
Gender					
Female	46.6	29.5	12.1	6.6	5.2
Male	60.3	20.8	9.8	5.2	3.9
Age (years)					
20–39	77.1	19.7	2.3	0.6	0.3
40–59	60.0	27.2	7.5	3.1	2.1
60–79	24.9	30.2	22.2	12.7	10.1
≥80	8.4	21.2	29.9	22.0	18.6
Scottish Index of Multiple Deprivation quintile					
1, least deprived	59.1	25.0	9.3	4.0	2.5
2	55.0	25.6	10.5	5.1	3.8
3	51.8	26.2	11.2	6.1	4.7
4	51.0	24.8	11.8	6.9	5.5
5, most deprived	50.5	24.1	11.9	7.3	6.2
Number of clinical conditions					
None	88.8	10.7	0.4	0.05	0.02
1	54.5	37.2	6.8	1.2	0.3
2	30.8	43.1	18.5	5.8	1.9
3	16.5	36.8	27.6	13.4	5.7
4 or 5	6.1	23.1	31.1	22.9	16.8
≥6	1.3	7.7	19.0	27.5	44.5

Table 2

Characteristics of patient population

Characteristic (n = 180 815)	Percentage of patients with one or more unplanned admission (n)
All patients	6% (10 828)
Gender	
Female (50.7%)	6.1% (5619)
Male (49.3%)	5.8% (5209)
Age (years)	
20–39 (30.9%)	3.2% (1797)
40–59 (37.9%)	3.9% (2679)
60–79 (25.0%)	8.7% (3943)
≥80 (6.2%)	21.4% (2409)
Scottish Index of Multiple Deprivation quintile	
1, least deprived (17.2%)	4.1% (1281)
2 (20.6%)	5.2% (1949)
3 (25.3%)	5.9% (2685)
4 (20.0%)	6.7% (2424)
5, most deprived (16.9%)	8.2% (2489)
Number of clinical conditions	
None (38.1%)	1.8% (1254)
1 (23.3%)	3.6% (1509)
2 (14.9%)	6.2% (1678)
3 (9.5%)	9.4% (1612)
4 or 5 (9.5%)	14.8% (2542)
≥6 (4.7%)	26.5% (2233)
Number of medications	
0 (53.3%)	2.8% (2736)
1–3 (25.2%)	5.2% (2356)
4–6 (11.0%)	10.3% (2043)
7–9 (5.9%)	15.4% (1647)
≥10 (4.6%)	24.8% (2046)

The mixed-effects multivariable logistic regression model shows that both the number of clinical conditions and the number of medications were associated with unplanned hospitalization, with evidence of a substantial negative interaction between the two ($P < 0.001$). In other words, the strength of the association between polypharmacy and unplanned admissions was greatly reduced in individuals with more conditions. Male gender, increasing age and socioeconomic deprivation were also all independently associated with increases in unplanned admission ($P < 0.001$). The random effect for practice provided strong evidence for modest variation in admission rates between practices ($P < 0.001$). Detailed results of the model are shown in Appendix 2.

The odds ratios presented in Appendix 2 are arguably not straightforward to interpret, owing to the inclusion of the interaction term in the model, and the nature of this association is better illustrated in Figure 1. This shows how the odds ratio for polypharmacy varies with number of medications for a given level of multimorbidity. For low levels of multimorbidity, there was a consistent increase in admission with increasing medication burden. For example, for patients with one recorded condition, the odds ratio for unplanned admission was 1.25 (95% CI 1.11–1.42) for four to six medications *vs.* one to three medications, and 3.42 (95% CI 2.72–4.28) for 10 or more medications *vs.* one to three medications. However, the most multimorbid patients (six or more conditions) taking four to six medications were no more likely to have an unplanned admission (OR 1.00; 95% CI 0.88–1.14) than those taking one to three medications, with a smaller increase in likelihood of admission in those taking 10 or more medications compared with those receiving one to three (OR 1.50; 95% CI 1.31–1.71). Interestingly, whilst patients with one condition and prescribed no regular medications were no more or less likely to be hospitalized compared with those receiving one to three medications (OR 0.99; 95% CI 0.91–1.07), those with six or more conditions receiving no medications were more likely to be admitted than those receiving one to three medications (OR 1.54; 95% CI 1.29–1.84).

The sensitivity analyses, using a weighted condition count based on the Charlson index or a subset of admissions, are presented in Appendix 3. The results of these analyses support the findings of the main multivariable model. Using a weighted condition count resulted in a relatively small change in the magnitude of effect of clinical condition count and number of medications. The same was generally true using potentially preventable unplanned admissions as the outcome variable, although the strength of association between the number of medications and hospitalization was increased.

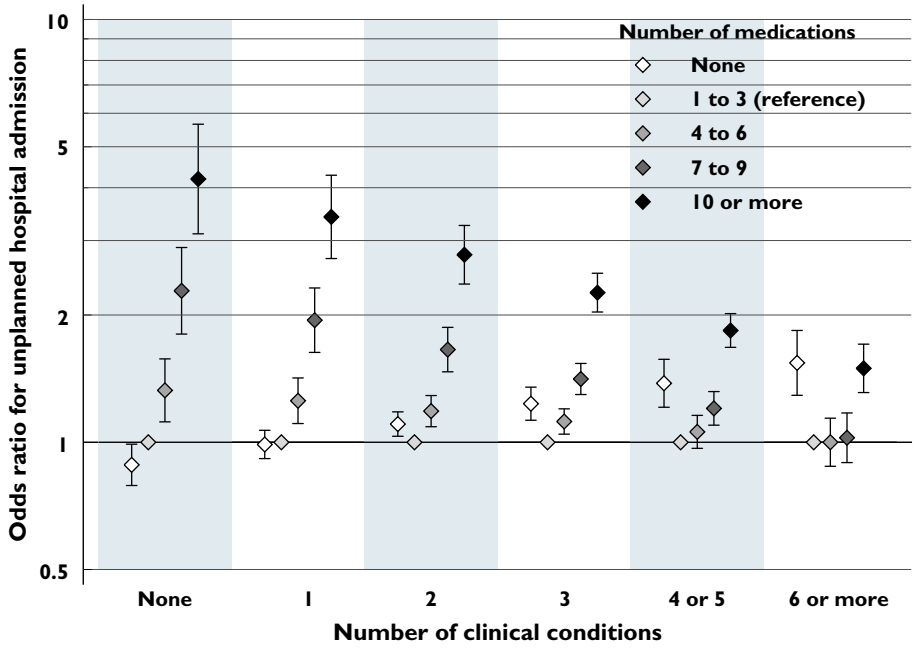

Figure 1

Adjusted odds ratios showing the association between admission and number of regular medications (relative to 1–3 regular medications), for different degrees of multimorbidity. For each number of clinical conditions, the clusters represent different numbers of medications, from none (white), through one to three, four to six, seven to nine, and 10 or more medications (black). Error bars are 95% confidence intervals. The point estimates shown in the figure can be calculated from the adjusted odds ratios reported in Appendix 2

Discussion

Polypharmacy is often considered to be undesirable. The present study demonstrates that polypharmacy is common and that it is associated with unplanned hospitalization. It also clearly shows that the association between polypharmacy and hospitalization is considerably reduced in individuals with multiple long-term conditions and that prescribing of multiple medications is associated with the greatest increased risk of unplanned hospitalization in those with fewest recorded conditions.

This study highlights the importance of considering polypharmacy in the clinical context for which medications are being prescribed, something that previous studies have not done. It demonstrates that both the presence and the degree of polypharmacy are important and that underprescribing is important to consider as well as overprescribing. Polypharmacy has been used both in admission prediction algorithms and as a quality indicator, but our analysis shows that this may be unwise unless the interplay between multimorbidity and medication utilization is appropriately taken into account.

Strengths and weaknesses

The main strengths of this study are its use of a large number of patients and a high-quality data set that is broadly representative of the population as a whole. Linkage to routine hospital data facilitates reliable identification of admissions, and the study captures almost all prescribing due to this being conducted almost exclusively in an electronic manner. Furthermore, unlike previous work, we have specifically examined the interaction between morbidity and medication burden. Of course, the study shares some of the limitations of similar observational studies. Firstly, we used a simple count of numbers of medications that were available for regular prescription. This does not capture the frequency with which prescriptions were issued, nor does it assess safety or appropriateness of medication. The latter factor may be better addressed by alternative measures, such as the Beers or STOPP criteria [18], although a straightforward count has the advantage of simplicity and is more readily determined. Secondly, we have no measure of disease severity, which may be an important confounding factor. However, there is a necessary trade-off between larger studies with routine data, such as ours, and smaller studies employing specially collected, detailed information but which may lack power to examine important questions. Furthermore, the effect modification observed suggests that drug count is not acting simply as a proxy for illness severity, because one might otherwise expect the magnitude of increase in admissions found with multiple medications to persist in those with multiple conditions. Thirdly, we do not know the reasons for particular admissions; although some

admissions may have been specifically medication related, the majority are probably not, and a causal relationship with polypharmacy cannot be determined in either case.

Comparison with previous work

Polypharmacy is common in persons admitted to hospital [19], and studies have shown that polypharmacy is associated with hospitalization for adverse drug reactions, accounting for a substantial minority of all admissions [10, 11]. Multimorbidity is a strong predictor of unplanned hospitalization [20], but studies have also shown that the number of medications that a patient is taking is of value in predicting admissions [21] and, indeed, may add to the predictive validity of other comorbidity measures [22].

However, the strength of the association between polypharmacy and hospitalization more generally has not been described in detail. Previous studies have been relatively small, limited to older patients, often treat polypharmacy as a binary variable, and do not account for the interaction between multimorbidity and number of medications. The Italian ULISSE project found that polypharmacy (five or more medications) in nursing home residents was associated with hospital admission (odds ratio 1.67) following adjustment for factors including comorbidity [13], although another Italian study found no such association in older, non-institutionalized patients [14]. A study in Western Australia reported hazard ratios of 1.04 for the association between the number of medications and both all-cause admission and death [12]. That study also noted that underutilization of medications may be problematic. Indeed, underprescribing is common [1], more frequently observed in the context of polypharmacy [23], and may contribute to hospitalization [24]. Our own study adds valuable additional information showing how the relationship between utilization of medication and hospitalization varies with multimorbidity. The association with more admissions in the most multimorbid individuals in receipt of no medicines also highlights the importance of avoiding underprescribing.

Policy implications

The potential importance of polypharmacy is well recognized by policy makers. The number of medications is incorporated in the widely used UK combined model for prediction of hospital admission [25], and polypharmacy is included as a quality indicator in the US Resident Assessment Instrument Minimum Data Set, a comprehensive, standardized tool to assess residents in long-term care [26]. There is an increasing realization that clinical guidelines, which are currently designed for single conditions, should address the clinical complexity of multimorbidity [27]. National guidance on managing polypharmacy has also been recently published in Scotland [28].

What is clear from our work is that the term 'polypharmacy' should not be misinterpreted as a characteristic of care that inevitably leads to adverse outcomes. Firstly, the number of medications should be evaluated across a range, and not crudely dichotomized as many studies have done in the past [29]. Secondly, it is important that the number of medications is considered together with the conditions for which they are prescribed and not in isolation. This may enable a more useful working definition of polypharmacy that would identify those potentially exposed to suboptimal prescribing. In addition, it may be possible to better identify individuals at higher risk of admission who may be suitable targets for interventions designed to improve care. In doing so, addressing the safe and rational use of medications may be important, including both underutilization and overutilization of drug therapy. However, it may also be worth examining broader aspects of clinical care that have been proposed as factors contributing to the use of multiple medications, such as lack of continuity of care, short consultation times and clinician anxiety [30].

Conclusions

This study provides powerful evidence that the number of regular medications is strongly associated with hospital admission. However, the effect is much reduced in patients with multiple conditions, in whom only the most extreme levels of polypharmacy are associated with an increase in unplanned hospitalization. Assumptions that polypharmacy is always unsafe or harmful and that it is indicative of suboptimal care need to be reconsidered in the clinical context of the conditions for which those drugs are being prescribed.

Authors' contributions

RAP conceived and designed the study. RAP and GAA carried out the data analysis. RAP wrote the first draft of the manuscript. All the authors contributed to interpretation of the data and revision of the manuscript. All the authors approved the final version of the manuscript. RAP had full access to all data in the study, had final responsibility to submit it for publication, and is the guarantor.

Conflicts of Interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Appendix 1

List of physical and mental health conditions included in condition count [3]

Physical conditions	Mental health conditions
Hypertension	Depression
Painful condition	Anxiety and other neurotic, stress-related and somatoform disorders
Asthma (currently treated)	Alcohol problems
Coronary heart disease	Other psychoactive substance misuse
Treated dyspepsia	Dementia
Diabetes	Schizophrenia (and related non-organic psychosis) or bipolar disorder
Thyroid disorders	Learning disability
Rheumatoid arthritis, other inflammatory polyarthropathies and systemic connective tissue disorders	Anorexia or bulimia
Hearing loss	
Chronic obstructive pulmonary disease	
Irritable bowel syndrome	
New diagnosis of cancer within last 5 years	
Treated constipation	
Stroke and transient ischaemic attack	
Chronic kidney disease	
Diverticular disease of intestine	
Atrial fibrillation	
Peripheral vascular disease	
Heart failure	
Prostate disorders	
Glaucoma	
Epilepsy (currently treated)	
Psoriasis or eczema	
Inflammatory bowel disease	
Migraine	
Blindness and low vision	
Chronic sinusitis	
Bronchiectasis	
Parkinson's disease	
Multiple sclerosis	
Viral hepatitis	
Chronic liver disease	

Appendix 2

Logistic regression models for unplanned hospital admission

	Unadjusted models Odds ratio (95% CI)	*P* value	Adjusted model*† Odds ratio (95% CI)	*P* value
Male	0.95 (0.92–0.99)	0.013	1.23 (1.18–1.28)	<0.001
Age	1.32 (1.30–1.34)	<0.001	1.05 (1.03–1.07)	<0.001
Age^2	1.07 (1.06–1.08)	<0.001	1.07 (1.06–1.07)	<0.001
Scottish Index of Multiple Deprivation				
1 (least deprived)	Reference	<0.001	Reference	<0.001
2	1.29 (1.20–1.38)		1.07 (0.99–1.16)	
3	1.45 (1.35–1.55)		1.19 (1.10–1.29)	
4	1.68 (1.56–1.80)		1.27 (1.17–1.38)	
5 (most deprived)	2.07 (1.93–2.22)		1.49 (1.36–1.62)	
Number of clinical conditions				
None	Reference	<0.001	Reference	<0.001
1	2.00 (1.86–2.16)		1.41 (1.25–1.59)	
2	3.58 (3.32–3.86)		1.74 (1.44–2.10)	
3	5.57 (5.16–6.01)		1.92 (1.50–2.46)	
4 or 5	9.37 (8.74–10.1)		2.32 (1.72–3.13)	
≥6	19.4 (18.0–20.9)		3.41 (2.45–4.75)	
Number of medications		<0.001		<0.001
None	0.54 (0.51–0.57)		0.88 (0.79–0.99)	
1–3	Reference		Reference	
4–6	2.11 (1.98–2.24)		1.33 (1.12–1.57)	
7–9	3.35 (3.13–3.58)		2.28 (1.80–2.89)	
≥10	6.04 (5.67–6.45)		4.19 (3.11–5.65)	

Appendix 2
Continued

	Unadjusted models Odds ratio (95% CI)	*P* value	Adjusted model*† Odds ratio (95% CI)	*P* value
Interaction between clinical conditions and number of medications				
Number of conditions × no medications	–		1.12 (1.06–1.18)	<0.001
Number of conditions × 4–6 medications	–		0.95 (0.90–1.00)	
Number of conditions × 7–9 medications	–		0.85 (0.80–0.91)	
Number of conditions × ≥10 medications	–		0.81 (0.75–0.88)	

The effect of age is given in terms of an odds ratio for a change of 10 years. *P* values are based on joint test of overall variability across categories. *Adjusted model includes a random effect for practice. Odds ratio for 95% midrange of practice variation (i.e. 2.5 and 97.5 percentiles, compared with average practice), 0.70–1.43, $P < 0.001$. †The odds ratios between unadjusted and adjusted models are not directly comparable, owing to the inclusion of the interaction term in the adjusted model. The adjusted odds ratios presented in this table were used to calculate the odds ratios and confidence intervals (CIs) presented in Figure 1, using the 'lincom' command in Stata. The point estimates in Figure 1 may also be calculated manually. For example, the odds ratio for admission to hospital for a person with three conditions and seven to nine medications (compared with a person with three conditions and one to three medications) is calculated as $2.28 \times 0.85^3 = 1.65$, where 2.28 and 0.85 are the respective odds ratios associated with a person with those characteristics, and 0.85 is cubed because there are three conditions. Note that confidence intervals cannot be calculated directly from this table because the covariance structure is not shown.

Appendix 3
Sensitivity analyses

	Adjusted model: weighted count of clinical conditions* Odds ratio (95% CI)	*P* value	Adjusted model: potentially preventable unplanned admissions† Odds ratio (95% CI)	*P* value
Male	1.15 (1.10–1.19)	<0.001	1.30 (1.19–1.42)	<0.001
Age	1.04 (1.02–1.06)	<0.001	1.00 (0.96–1.04)	0.83
Age^2	1.06 (1.06–1.07)	<0.001	1.06 (1.05–1.07)	<0.001
Scottish Index of Multiple Deprivation				
1 (least deprived)	Reference	<0.001	Reference	<0.001
2	1.09 (1.00–1.18)		1.28 (1.06–1.55)	
3	1.22 (1.13–1.32)		1.51 (1.26–1.82)	
4	1.32 (1.22–1.44)		1.48 (1.22–1.80)	
5 (most deprived)	1.61 (1.48–1.75)		1.76 (1.45–2.13)	
Number of clinical conditions				
None	Reference	<0.001	Reference	<0.001
1	1.31 (1.20–1.42)		1.54 (1.13–2.11)	
2	1.59 (1.41–1.79)		2.04 (1.34–3.10)	
3	1.70 (1.46–1.98)		2.22 (1.33–3.72)	
4 or 5	2.09 (1.76–2.48)		2.67 (1.49–4.80)	
≥6	3.05 (2.43–3.83)		3.94 (2.12–7.34)	
Number of medications				
None	0.65 (0.61–0.70)	<0.001	0.59 (0.44–0.81)	<0.001
1–3	Reference		Reference	
4–6	1.50 (1.37–1.65)		2.01 (1.36–2.97)	
7–9	2.35 (2.09–2.64)		2.37 (1.40–4.00)	
≥10	3.80 (3.33–4.34)		7.95 (4.56–13.86)	
Interaction between clinical conditions and number of medications				
Number of conditions × no medications	1.25 (1.17–1.33)	<0.001	1.13 (0.98–1.29)	0.007
Number of conditions × 4–6 medications	0.87 (0.82–0.92)		0.90 (0.79–1.01)	
Number of conditions × 7–9 medications	0.76 (0.72–0.81)		0.94 (0.82–1.09)	
Number of conditions × ≥10 medications	0.76 (0.71–0.81)		0.82 (0.71–0.95)	

The effect of age is given in terms of an odds ratio for a change of 10 years. *P* values are based on joint test of overall variability across categories. *An additional model was constructed by replacing the simple clinical condition count with a weighted count of certain conditions based on the original Charlson index [31]. This index is weighted based on mortality. A pragmatic approach was used in developing modified weightings, because the list of conditions included in the Charlson index is not concordant with the list of 40 conditions included in our own analysis. For example, we cannot include HIV/AIDS (albeit rare in Scotland, and probably less strongly associated with admission since highly active antiretroviral therapy use became routine) and are unable to distinguish solid/blood cancers, severity of liver disease, complications of diabetes, or hemiplegia resulting from stroke. The following conditions were included to create a weighted count (weightings in parentheses as per the original Charlson index): ischaemic heart disease (1), heart failure (1), stroke (1), dementia (1), chronic obstructive pulmonary disease (1), connective tissue/rheumatological conditions (1), viral hepatitis or chronic liver disease (1), diabetes (1), chronic kidney disease (2) and cancer (2). †A further model was constructed to examine the alternative outcome of potentially preventable unplanned admissions, which are a subset of the main outcome. Potentially preventable admissions are those for conditions which are considered most preventable by better primary and outpatient care, and were defined using a standard NHS Scotland list [32].

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